Heritability of Head Size in Dutch and Australian Twin Families at Ages 0–50 Years

Dirk J. A. Smit,[1] Michelle Luciano,[2,3] Meike Bartels,[1] Catharine E. M. van Beijsterveldt,[1] Margaret J. Wright,[2] Narelle K. Hansell,[2] Han G. Brunner[4], G. Frederiek Estourgie-van Burk,[1,5] Eco J. C. de Geus,[1] Nicholas G. Martin[2] and Dorret I. Boomsma[1]

[1] *Department of Biological Psychology, VU University, Amsterdam, The Netherlands*
[2] *Queensland Institute Medical Research & University of Queensland, Brisbane, Australia*
[3] *Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, United Kingdom*
[4] *Radboud University, Medical Center Department of Human Genetics, Nijmegen, The Netherlands*
[5] *Department of Pediatrics, VU Medical Centre, Amsterdam, The Netherlands*

We assessed the heritability of head circumference, an approximation of brain size, in twin-sib families of different ages. Data from the youngest participants were collected a few weeks after birth and from the oldest participants around age 50 years. In nearly all age groups the largest part of the variation in head circumference was explained by genetic differences. Heritability estimates were 90% in young infants (4 to 5 months), 85–88% in early childhood, 83–87% in adolescence, 75% in young and mid adulthood. In infants younger than 3 months, heritability was very low or absent. Quantitative sex differences in heritability were observed in 15- and 18-year-olds, but there was no evidence for qualitative sex differences, that is, the same genes were expressed in both males and females. Longitudinal analysis of the data between 5, 7, and 18 years of age showed high genetic stability ($.78 > R_G > .98$). These results indicate that head circumference is a highly heritable biometric trait and a valid target for future GWA studies.

Keywords: twin study, brain size, head circumference, infant growth

The measurement of head size gives an approximation of brain size (Cooke et al., 2000) as in humans the fetal and postnatal skull bones enlarge because of outward pressure from the growing brain (Tanner, 1989; Woods, 2004). Most of the craniofacial bones are, in contrast to other parts of the skeleton, of neural crest origin (Wilkie & Morriss-Kay, 2001). It is relatively well established that genetic factors contribute significantly to the variation of head size, although several questions remain regarding the genetic architecture of head size (e.g., Eaves et al., 2005). These include questions of whether the effects of multiple genes are additive; whether genetic effects depend on sex (e.g., whether different genes affect males and females or whether the same genes are expressed in both sexes but to different degrees); and how the effects of genes unfold over time.

Data on resemblance in head size from parent-offspring and from sibling studies suggest substantial additive genetic effects and no or only small nonadditive genetic effects. Nonadditive genetic effects would be suggested if resemblance of parents and offspring is less than resemblance among siblings. Ermakov et al. (2005) report for data that were collected in a large series of Chusvasa pedigrees, a parent–offspring correlation of 0.36 for adjusted head circumference and a sibling correlation of 0.37.

Sex differences in genetic architecture have sometimes been reported for craniofacial characteristics — for example, a large Icelandic study of parents and offspring (Johannsdottir et al., 2005) and a small Belgian twin study (Carels et al., 2001). However, both maternal and paternal height predicted fetal growth, including head circumference, in a longitudinal growth study of children from Exeter in the United Kingdom (Knight et al., 2005) and in a smaller Chilean sample (Ivanovic et al., 2004).

From a developmental perspective, head size at a particular age may reflect different growth trajectories influenced by different experiences and/or genetic factors during sensitive periods of brain development. For example, a child whose brain growth pre- and postnatally followed the 50th centile might attain the same head size as a child whose brain growth was initially slow, but who later experienced rapid growth (Gale et al., 2004). Many pre- and perinatal factors may influence head circumference at birth. Gestational age is perhaps the largest factor in determining birth weight and head circumference (Buckler & Green, 1994; Green & Buckler, 2008). Whether these effects fully disappear after the catch-up growth of preterm infants (Euser et al., 2008; Estourgie-van Burk et al., 2009) is unknown.

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Address for correspondence: Dirk J.A. Smit, van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. E-mail: dja.smit@psy.vu.nl

To examine the genetic architecture of individual differences of head circumference, including sex and developmental effects, we analyzed data from several twin-sibling studies, carried out in The Netherlands and in Australia. Twin studies offer the possibility to obtain estimates of additive and nonadditive components of variance, and to distinguish between sources of familial resemblance that are caused by shared genes and by shared environment (Martin et al., 1997). The high parent–offspring and sibling correlations observed in pedigree studies are consistent with a high additive genetic heritability, but could also derive from shared environmental, non-genetic, factors. For example, the correlation between IQ and head size as reported in several studies may point to a mechanism by which cognitive stimulation by parents promotes both cognitive development and brain growth (Gale et al., 2004). Siblings who grow up in the same home and who are exposed to the same extent and quality of parental stimulation may through these mechanisms show similarity in head size. How important such a mechanism might be and whether it explains any of the individual differences in head circumference is unclear. If variation in head size reflects cognitive stimulation, we may expect familial resemblances at younger ages to reflect shared environmental influences, as these influences explain most of the variation in IQ scores in young children (Bartels et al., 2002).

In this article we look at head circumference data from monozygotic and dizygotic twins and siblings of twins from two sources. First, we analyzed head circumference data from twins assessed at very young ages during visits to Youth Health Services clinics. Head circumference is often recorded during these visits in order to track physical growth. Second, we analyzed data from subjects who participated in EEG research projects. EEG measurements require careful assessment of head circumference as part of the systematic placement of the electrodes on the skull (Pivik et al., 1993). Head circumference in the youngest age groups was assessed at ages 5 and 7 years, a subsample of whom returned at age 18 with additional siblings. Adolescent twins were assessed at ages 15 and 17 years. A second group of adolescent 16-year-old twins was assessed once, and included an additional sibling in some families. Two groups of adult twins and their siblings participated around age 25 and 50 years. These data were analyzed to estimate heritability for variation in head circumference and to test, especially at younger ages, if shared environment contributes to twin and sibling resemblance. Next, we tested if there are sex differences in genetic architecture (e.g., Is heritability more important in girls and shared environment more important in boys?). Finally, we tested whether the genes involved are the same in childhood and young adulthood by the use of a long-term longitudinal data set.

Method

Participants

Several projects in the Netherlands and in Australia contributed data on head circumference. Tables 1 and 2 give an overview of the number of twins, the number of pairs and the number of siblings in the different samples.

Dutch Sample I (infancy, childhood, and young adulthood): Five-year old twins were recruited from the Netherlands Twin Register (Boomsma et al., 2002). At age 5, 209 twin pairs participated. At age 7, 192 pairs came back for a second time. At age 18, 121 pairs of the original set returned. Up to two singleton siblings were additionally invited to participate at this age and 102 accepted the invitation. In addition, twins and siblings from previously untested families were measured. When they were 5 and 7 year old, these children took part in a study of IQ and brain function, assessed with EEG and ERP parameters (Van Baal et al., 1996) and cognition (Boomsma and van Baal, 1996). There was no significant IQ difference at age 5 between children who participated and children who did not participate the second time. For 161 same-sex twin pairs zygosity was determined by blood group/DNA typing (48 blood groups, 113 DNA typing). For the remaining 8 pairs, zygosity was determined from questionnaire items. As young adults a substantial number of these twins took part in a study of genetic influences on physical and hormonal development (Estourgie-van Burk et al., 2009). To increase sample size, an invitation was sent to twins who had not previously taken part in IQ studies, and to the siblings of all twin pairs (if present). At this time we collected from the mothers data on the twins recorded during visits to the Youth Health Service Clinics. We asked for the age of the twins at the times head circumference data were measured. As children visit the clinics at different ages, the data were grouped into five age groups: 0 and 1 months, 2 and 3 months, 4 and 5 months, 6 to 8 months, and 9 to 13 months. If multiple observations were available within a period (e.g., when weekly measurements were taken) both the average age and head circumference were taken. Data were analyzed univariately with and without pregnancy duration (gestational age at birth) as a covariate.

Dutch Sample II (adolescents): A sample of 213 adolescent twin pairs participated twice in a study of brain function (Van Beijsterveldt et al., 2001). The mean interval between sessions was 1.5 years. There were 19 twin pairs who did not return for the second test session. The mean age of the twins at the first test session was 16.2 years (SD = 0.55) and at the second session 17.6 years (SD = 0.54). Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behavior (Boomsma et al., 1994). For 114 same-sex twin pairs zygosity was determined by blood or DNA typing. For the other same-sex twins zygosity was determined based

on a questionnaire that was completed by the mother. In 17 twin pairs zygosity was determined based on a questionnaire that they completed themselves. Agreement between zygosity based on this questionnaire and zygosity based on blood group polymorphism was 95%.

Dutch Sample III (adults): From a total of 309 extended twin families, 760 family members were recruited from the Netherlands Twin Registry to participate in a study on the genetics of cognition and adult brain function (Smit et al., 2005; Posthuma et al., 2001). A maximum of four singleton siblings per family was imposed to simplify analyses, hence the data of four individuals were excluded. The sample comprised two cohorts based on the age of the twins (young cohort under 36 years of age, older cohort 36 years or above). The mean age of the young cohort was 25.8 (± 2.9) years and the mean age of the older cohort was 49.4 (± 6.8) years. There was a slight overlap in age of the non-twin siblings between the two cohorts. The number of participating family members ranged from one to six with most families consisting of a twin pair without siblings. Zygosity was determined by genotyping for 205 out of 246 same sex twin families, with the remainder determined by questionnaire data.

Australian Sample (adolescents): From the Genes for Cognition twin study (Wright & Martin, 2004), 644 twin pairs and 163 of their non-twin siblings, plus two pairs of non-twin siblings were included in the present study. Most twins had participated in a melanocytic naevi study 2 years earlier (Zhu et al., 1999) and others were ascertained through mail-outs to secondary schools in the Brisbane region. Head circumference was collected as part of ERP and EEG recording sessions (e.g., Hansell et al. 2001; Zietsch et al., 2007). Zygosity was determined by ABO, MN and Rh blood groups and by 9 independent polymorphic DNA markers of the ABI Profiler Plus Kit; probability of error less than 10^{-4}. The twins were mostly in their penultimate year of secondary school and aged between 15 and 18 years (16.2 years ± 0.4), their siblings were aged between 15 and 22 years (17.4 years ± 1.1).

Exclusion Criteria and Informed Consent

Participants had been excluded if they had a history of significant head injury, neurological or psychiatric illness, substance dependence, or if they were currently taking long term medications with central nervous system effects. Participants had normal or corrected-to-normal vision (better than 6/12 Snellen equivalent). Written informed consent was obtained from the participants, and from their parents/guardian if they were a minor, prior to testing.

Measures

Head circumference was measured around fixed anatomical points (over the occiput and just above the eyebrows and ears).

Statistical Procedure

Within each sample familial resemblance for head size was summarized with correlation coefficients. Maximum likelihood estimates of correlations were computed in Mx (Neale et al. 2006). In samples which consisted of twins and siblings, correlations were equated between DZ, sibling and twin-sib pairs. Correlations were estimated separately for male–male, female–female and opposite-sex pairs. Depending on the pattern of MZ–DZ correlations, genetic models tested the extent to which familial resemblance could be ascribed to additive genetic influences ('A'), genetic nonadditivity (Dominance 'D'), or environmental factors common to family members ('C'). Within MZ pairs, dissimilarity is attributed to unique environmental influences ('E'). Within DZ and sibling pairs, dissimilarity is caused both by unique environment and nonshared genetic influences. Genetic models were fitted to raw data in Mx (Neale et al. 2006). Fixed effects of sex and age were incorporated in the model for the mean effects.

The procedure for testing for sex differences was as follows. First we fitted a saturated model in which correlations were estimated for monozygotic male and female (MZM, MZF), dizygotic male and female (DZM, DZF) and DZ opposite-sex (DOS) pairs. Next, this model was compared to an ACE or ADE model that estimated the effects of A, D/C, and E without sex differences. If this model fitted significantly worse than the saturated model, we examined whether sex differences were present for the A, D/C, and E path loadings. We also tested for the presence of qualitative sex differences (a genetic correlation between males and females being less than 0.5). As a final step, the effect of A, and/or D/C was dropped from the model (with or without sex differences, depending on previous results). Simpler nested models (e.g., AE) were compared to more complex models (e.g. ACE) with likelihood-ratio chi-squared test. Doubling the negative log likelihood allows model comparisons since twice the difference in negative log likelihood between models is distributed (asymptotically) as χ^2.

Longitudinal genetic models were applied to the repeated measures of head circumference in sample I between ages 5, 7, and 18. These models decompose the variances at each age and the covariance across age into genetic and nongenetic components. Genetic and environmental components of covariance can be standardized to obtain genetic and environmental correlations that reflect stability of genetic and environmental factors across time. The information for the decomposition of the covariance structure across time comes from the twin-sib cross-correlations (e.g., head size in twin 1 at Time 1 with head size in twin 2 at Time 2).

Results

Descriptive statistics (means and standard deviations) and sample size statistics are given for each age group in Table 1.

Infancy Twin Correlations

Infancy twin correlations were estimated in saturated models with age in months and sex as covariates. Table 2 shows the twin correlations with (right column) and without (left column) correction for pregnancy duration. The effect of gestational age was significant as a regressor on head circumference for age groups 2–3 months, $\chi^2(1) = 5.14$, $p = .023$) and 9–13 months, $\chi^2(1) = 6.96$, $p = .008$. Nevertheless, the correction for pregnancy duration hardly changed the twin correlations. MZ correlations were invariably high. DZ correlations were close to MZ correlations for the two youngest age groups, both corrected and uncorrected, suggesting effects of shared environment (common environment, C) at these ages. DZ correlations sharply dropped for age groups 4 months and older, suggesting a switch from strong common environmental effects to high heritability. Figure 1 illustrates this effect by plotting the development of MZ and DZ correlations over the first year of life.

Table 3 shows model fit statistics for the infant data. Sex differences were not modeled, because of low number of twin pairs available. The results show significant C effects at the two youngest age groups (under 4 months). Note that these C effects were obtained after correcting for pregnancy duration and may therefore include only other common environmental effects. From the age of 4 months, the effect of A was high and significant. The standardized estimates of the variance attributable to A, C, and E with 95% confidence intervals are shown in Table 4.

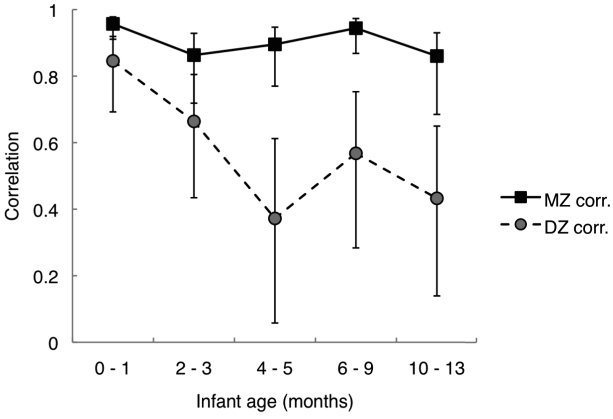

Figure 1

Development of MZ and DZ twin correlation from 0 to 13 months with correction for pregnancy duration. error bars are 95% confidence intervals.

Childhood, Adolescent, and Adult Twin-Sibling Correlations

MZ and DZ/sib correlations are summarized in Table 5. As may be seen, MZ correlations were higher than DZ correlations in childhood and older age groups and this pattern of correlations suggests a high heritability. There is some evidence that non-additive genetic factors were of importance in older age groups, and therefore an ADE model was fitted to these data. Figure 2 is a graphical depiction of the development of the MZ and DZ correlations with 95% confidence intervals.

Table 6 gives model-fitting results (goodness of fit). There was some evidence of sex differences in the

Table 1

Descriptions (*N*, Average Head Circumference in cm, Standard Deviations) by Age and Zygosity Group

		MZ		DZ		Siblings	
Age group	Sample	*N*	*M* (SD)	*N*	*M* (SD)	*N*	*M* (SD)
Infancy							
0–1	I (NL)	73	35.1 (2.54)	96	36.2 (2.16)	—	—
2–3	I (NL)	68	39.5 (1.48)	96	40.0 (1.45)	—	—
4–5	I (NL)	64	42.2 (1.13)	94	42.2 (1.41)	—	—
6–8	I (NL)	63	44.1 (1.33)	85	44.4 (1.42)	—	—
9–13	I (NL)	72	46.3 (1.26)	115	46.4 (1.49)	—	—
Childhood and older							
5	I (NL)	178	51.9 (1.23)	240	51.6 (1.38)	—	—
7	I (NL)	158	52.5 (1.27)	226	52.3 (1.43)	—	—
15	II (NL)	175	55.3 (1.62)	234	55.7 (1.57)	—	—
16	III (AU)	257	56.7 (1.74)	370	56.8 (1.53)	74	57.3 (1.59)
17	II (NL)	161	55.7 (1.63)	214	56.1 (1.67)	—	—
18	I (NL)	192	56.1 (1.46)	264	56.3 (2.00)	96	56.2 (2.14)
25	IV (NL)	124	56.4 (2.07)	161	56.7 (1.90)	100	57.0 (1.63)
50	IV (NL)	138	56.6 (2.32)	138	56.6 (2.13)	76	56.9 (2.09)

Note : NL = Netherlands, AU = Australia.

Table 2

Infancy Twin Correlations With 95% Confidence Intervals

	Uncorrected		Corrected for pregnancy duration	
Age group	MZ	DZ	MZ	DZ
0–1	0.96 (0.91, 0.978)	0.85 (0.69, 0.919)	0.96 (0.91, 0.978)	0.85 (0.70, 0.921)
2–3	0.86 (0.72, 0.929)	0.66 (0.43, 0.805)	0.85 (0.70, 0.924)	0.66 (0.42, 0.802)
4–5	0.90 (0.77, 0.947)	0.37 (0.06, 0.612)	0.89 (0.76, 0.944)	0.33 (0.01, 0.585)
6–9	0.94 (0.87, 0.973)	0.57 (0.28, 0.753)	0.94 (0.86, 0.971)	0.51 (0.21, 0.724)
10–13	0.86 (0.68, 0.930)	0.43 (0.14, 0.650)	0.85 (0.66, 0.924)	0.44 (0.15, 0.655)

Table 3

Univariate Model Fit of Headsize for Infants Aged 0 to 13 Months Testing ACE Decomposition

Age group	Model		–2LL	*df*	Compare model	χ^2	Δdf	*p*
0–1 months								
	1	**ACE**	**350.06**	**91**				
	2	AE	368.53	92	1	18.47	1	0.000
	3	CE	356.06	92	1	6.00	1	0.014
	4	E	446.47	93	1	96.40	2	0.000
2–3 months								
	5	ACE	311.67	101				
	6	AE	316.41	102	5	4.74	1	0.029
	7	**CE**	**313.00**	**102**	**5**	**1.33**	**1**	**0.248**
	8	E	350.40	103	7	37.40	1	0.000
4–5 months								
	9	ACE	274.13	91				
	10	**AE**	**274.13**	**92**	**9**	**0.00**	**1**	**1.000**
	11	CE	289.69	92	9	15.57	1	0.000
	12	E	302.75	93	10	28.62	1	0.000
6–9 months								
	13	ACE	259.12	83				
	14	**AE**	**259.14**	**84**	**13**	**0.02**	**1**	**0.877**
	15	CE	272.47	84	13	13.35	1	0.000
	16	E	289.15	85	14	16.69	1	0.000
9–13 months								
	17	ACE	308.84	95				
	18	**AE**	**309.20**	**96**	**17**	**0.37**	**1**	**0.546**
	19	CE	314.80	96	17	5.96	1	0.015
	20	E	336.52	97	17	21.73	1	0.000

Note: All models had age, sex, and pregnancy duration covariates. Boldface models are best-fitting models..

Table 4

Infant Age Group Genetic, Common and Unique Environment Effects From the Best Fitting Model with 95% Confidence Intervals

Age (months)	A	C	E
0–1	0.14 (0.03, 0.35)	0.82 (0.61, 0.92)	0.04 (0.02, 0.08)
2–3	—	0.71 (0.55, 0.82)	0.29 (0.18, 0.45)
4–5	0.90 (0.77, 0.95)	—	0.10 (0.05, 0.23)
6–8	0.92 (0.82, 0.96)	—	0.08 (0.04, 0.18)
9–13	0.84 (0.66, 0.92)	—	0.16 (0.08, 0.34)

Note: All models had age, sex, and pregnancy duration covariates.

Table 5a

Dutch Sample age 5, 7, and 18, Twin Correlations From the Saturated Models With 95% Confidence Intervals. *N* Denotes the Number of Complete Twin Pairs (Plus the Total Number of Twin–Sibling and Sibling–Sibling Relations for Age 18)

Twin correlation	Age 5	Age 7	Age 18
MZM	0.81 [0.70, 0.88] (*N* = 42)	0.84 [0.72, 0.90] (*N* = 37)	0.81 [0.70, 0.87] (*N* = 32)
DZM	0.40 [0.12, 0.61] (*N* = 44)	0.54 [0.28, 0.71] (*N* = 41)	0.60 [0.44, 0.71] (*N* = 31+48)
MZF	0.87 [0.78, 0.92] (*N* = 47)	0.91 [0.85, 0.94] (*N* = 42)	0.84 [0.73, 0.90] (*N* = 44)
DZF	0.57 [0.31, 0.73] (*N* = 37)	0.47 [0.17, 0.67] (*N* = 34)	0.38 [0.20, 0.53] (*N* = 36+75)
OS	0.36 [0.09, 0.56] (*N* = 39)	0.49 [0.25, 0.66] (*N* = 38)	0.53 [0.41, 0.63] (*N* = 34+80)

Note: MZM = monozygotic male; DZM = dizygotic male; MZF = monozygotic female; DZF = dizygotic female; OS = oppostie sex.

Table 5b

Dutch Sample Ages 15 and 17, Twin Correlations From the Saturated Models With 95% Confidence Intervals — *N* Denotes the Number of Complete Twin Pairs

Twin correlation	Age 15	Age 17
MZM	0.79 [0.65, 0.87] (*N* = 37)	0.88 [0.79, 0.93] (*N* = 35)
DZM	0.44 [0.14, 0.65] (*N* = 32)	0.46 [0.19, 0.66] (*N* = 28)
MZF	0.92 [0.87, 0.95] (*N* = 48)	0.89 [0.82, 0.93] (*N* = 43)
DZF	0.43 [0.15, 0.62] (*N* = 37)	0.34 [0.04, 0.56] (*N* = 35)
OS	0.57 [0.30, 0.73] (*N* = 43)	0.46 [0.05, 0.68] (*N* = 39)

Note: Abbreviations see Table 5a.

Table 5c

Australian Sample Age 16, Twin Correlations From the Saturated Models With 95% Confidence Intervals — *N* Denotes the Number of Complete Twin Pairs Plus the Total Number of Twin–Sibling and Sibling–Sibling Relations

	Age 16
MZM	0.80 [0.74–0.84] (130)
DZM	0.32 [0.16–0.45] (91 + 81)
MZF	0.79 [0.73–0.83] (144)
DZF	0.20 [0.05–0.34] (90 + 100)
OS	0.42 [0.31–0.51] (189 + 163)

Note: abbreviations see Table 5a.

Table 5d

Dutch Samples ages 25 and 50, Twin Correlations From the Saturated Models with 95% Confidence Intervals — *N* Denotes the Number of Complete Twin Pairs Plus the Total Number of Twin–Sibling and Sibling–Sibling Relations

	Age ~25	Age ~50
MZM	0.79 [0.65, 0.86] (*N* = 29)	0.73 [0.51, 0.84] (*N* = 27)
DZM	0.23 [0.01, 0.45] (*N* = 21+58)	0.49 [0.19, 0.68] (*N* = 11 + 30)
MZF	0.70 [0.49, 0.81] (*N* = 30)	0.76 [0.63, 0.85] (*N* = 40)
DZF	0.15 [–0.20, 0.45] (*N* = 28+61)	0.14 [–0.21, 0.45] (*N* = 30 + 56)
OS	0.49 [0.34, 0.61] (*N* = 25+67)	0.31 [0.10, 0.48] (*N* = 23+63)

Note: Abbreviations see Table 5a.

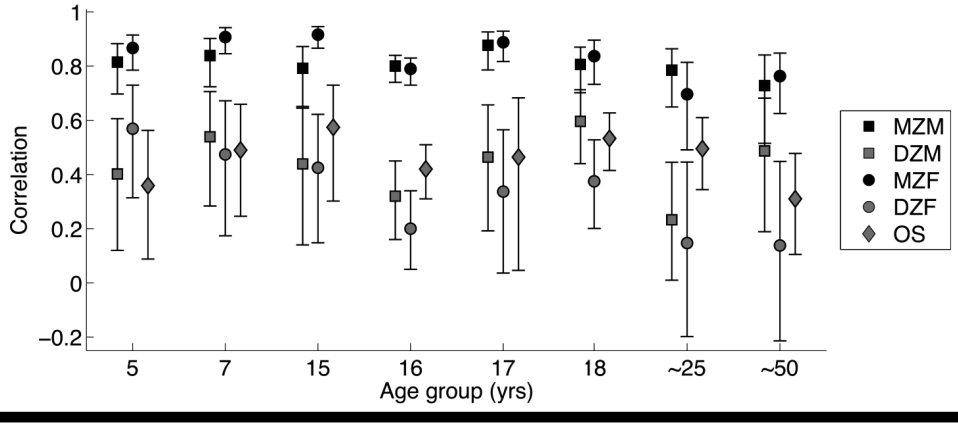

Figure 2

Monozygotic male (MZM), dizygotic male (DZM), monozygotic female (MZF), dizygotic female (DZF), and opposite sex (OS) twin correlation development from 5 to 50 years. Dizygotic correlations also include all male–male, female–female, and opposite sex twin–sibling and sibling–sibling relations whenever available. Error bars are 95% confidence intervals.

Table 6

Univariate Model Fit of Headsize Split by Age Group for Childhood, Adolescent, and Adult Age Groups

Age group		Model	–2LL	*df*	Compare model	χ^2	Δdf	*p*
Age 5 (NL)	1	ACE (no sex diffs*)	1235.58	406				
	2	**AE**	**1238.35**	**411**	**1**	**2.78**	**5**	**0.735**
Age 7 (NL)	3	ACE (no sex diffs*)	1138.93	372				
	4	**AE**	**1142.71**	**377**	**3**	**3.78**	**5**	**0.582**
Age 15 (NL)	5	ACE with sex diff	1324.039	399				
	6	ACE without sex diff, rG free	1334.202	402	5	10.16	3	0.017
	7	ACE with sex diff, rG = 0.5	1324.039	400	5	0.00	1	1.000
	8	**AE with sex diff, rG free**	**1324.436**	**402**	**7**	**0.40**	**2**	**0.820**
Age 16 (Au)	9	ACE (no sex diffs *)	5284.222	1434				
	10	**AE**	**5284.222**	**1435**	**9**	**0.00**	**1**	**1.000**
Age 17 (NL)	11	ACE (no sex diffs *)	1201.43	357				
	12	**AE**	**1201.74**	**362**	**11**	**0.31**	**1**	**0.578**
Age 18 (NL)	13	ACE with sex diff	1877.75	531				
	14	ACE without sex diff, rG free	1891.894	534	13	14.14	3	0.003
	15	ACE with sex diff, rG = 0.5	1877.75	532	13	0.00	1	1.000
	16	**AE with sex diff**	**1883.415**	**534**	**15**	**5.66**	**2**	**0.059**
Age 25 (NL)	17	ADE (no sex diffs *)	1361.324	379				
	18	**AE**	**1363.884**	**380**	**17**	**2.56**	**1**	**0.110**
Age 50 (NL)	19	ADE (no sex diffs *)	1275.273	346				
	20	**AE**	**1275.273**	**347**	**19**	**0.00**	**1**	**1.000**

Note: All models had age and sex regression on the mean. Sex differences were first tested in an omnibus test against the saturated model estimating 5 correlations. When not significant, C/D was dropped form the ACE (ages below 25) or ADE model (ages 25 and 50) without sex differences. When the omnibus test for sex differences was significant, the model was subdivdided in testing significant sex differences in variance components and genetic overlap between the sexes before testing significance of C. The significant sex differences were retained. Boldface models are best-fitting models.

* Model not significantly worse than saturated.

variance decomposition at ages 15 and 18, but no evidence that different genes operate in males and females at these ages or any other age (viz., setting the correlation between the male and female genetic factors to 0.5 did not significantly worsen the model fit). Table 7 summarizes the ML estimates of heritability from the best fitting models. Note that the confidence intervals suggests no sex differences in the heritability estimates for the age 18 group. This suggests that the sex differences that were found are differences in variances, not in the standardized heritability.

The longitudinal model was fit with sex differences in variance decomposition and with the genetic correlation between genetic factors expressed in men and women fixed at 0.5. The results are shown in Table 8. Genetic stability was high in both sexes, even at an age range of 5 to 18 years ($.78 < R_G < .92$), which includes periods of large head volume increases. Genetic stability in men was significantly higher than in women as evidenced by the confidence intervals. Short-range (2 year) genetic stability is close to unity (.98). Note that environmental factors also show some level of stability ($.50 < R_E < .82$), suggesting that

Table 7

Heritabilities for Childhood, Adolescent and Adult Age Groups

	h^2	95% CI
5	0.84	(0.78, 0.89)
7	0.88	(0.82, 0.91)
15 (Male/Female)	0.79 / 0.92	(0.67, 0.87) / (0.86, 0.94)
16	0.83	(0.79, 0.86)
17	0.88	(0.83, 0.92)
18 (Male/Female)	0.81 / 0.84	(0.73, 0.87) / (0.74, 0.90)
25	0.74	(0.64, 0.82)
50	0.75	(0.64, 0.82)

Table 8

Genetic and Environmental Stability with 95% Confidence Intervals

	Male		Female	
	R_G	R_E	R_G	R_E
Short range				
5 to 7	0.98 (0.96, 0.998)	0.71 (0.55, 0.82)	0.97 (0.95, 0.99)	0.70 (0.53, 0.82)
Long range				
5 to 18	0.86 (0.77, 0.92)	0.62 (0.39, 0.77)	0.78 (0.69, 0.86)	0.67 (0.37, 0.82)
7 to 18	0.92 (0.85, 0.97)	0.50 (0.23, 0.70)	0.81 (0.72, 0.88)	0.51 (0.18, 0.72)

unique factors influencing head circumference before the age of 5 are still visible at 18, and — possibly — the rest of life. Such factors could include disease, accidents, but could also point to asymmetric development of the twins in utero that persist.

Discussion

The present study shows that the heritability of head size was large, was the same in children, adolescents and adults and was the same in Australian and Dutch adolescent twins. These results agree with those from smaller scaled twin studies of total brain volume assessed from structural MRI recordings. Typically these studies report heritabilities of 80% or higher for total brain volume (Peper et al., 2009; Schmitt et al., 2007; Toga & Thompson, 2005). The only study to look at older ages was by Geschwind et al. (2002), that looked at 72 MZ and 67 DZ older male twin pairs and reported a lower heritability of 60% for volume of each cerebral hemisphere and 61% for total cerebral hemispheres. These lower heritabilities may reflect age-related changes in brain volumes that are only partially under genetic control.

No large or systematic effects of sex on genetic makeup for head circumference were found. The effects were restricted to the age groups 15 and 18 where the (unstandardized) variance decomposition differed between males and females. The difference was restricted to the absolute size of path loadings of the genetic and unique environmental factors; there was no evidence for different sets of genes playing a role in males and females at these or other ages. The (standardized) heritability estimates were significantly different between the sexes at age 15 only.

Infancy head circumference measurements showed a possible role for common environmental factors but only at the earliest stages in life. These effects remained after taking pregnancy duration into account. Although pregnancy duration did show a significant effect on the average head circumference, this did not result in significantly different results in the variance decomposition. Overall, these results suggest that common environmental effects on head circumference other than pregnancy duration play an important role in the earliest stages of life but quickly give way to subsequent growth that is highly genetically determined.

The childhood-to-adolescence longitudinal analysis showed that the genetic correlation over a period of two years was almost perfect (r_G ~1.0), and high across a period of more than a decade (r_G >.78 in females, r_G > .85 in males). These results suggest that individual differences in head circumference are not only a highly genetic trait from cradle to grave, but also genetically highly stable. The common environmental effect that existed at birth disappeared very early in life (at 4 months), and does not seem to be related to pregnancy duration — an otherwise prominent factor in twin births (Green and Buckler, 2008). Therefore, the current results bode well for future gene hunting studies, such as genome wide association. Data from a large age range as well as from both sexes can be pooled to in the effort of pinpointing genes that are involved in head growth and the related measure of brain size.

Environmental factors have been reported to influence head circumference at birth. For example, the world trade center (9/11) prenatal stress and/or pollutant exposure in women in first trimester during the attacks delivered babies with smaller head circumference (Lederman et al., 2004). Such adverse circumstances, however, may not play a large role unless they are severe (terrorist attacks, Ledermann et al; arrest of spouse, Obel et al., 2003). Also, it is unknown if these initial differences persist beyond the first year of life. The current results suggest that in a population based sample of twins these effects are restricted to the first year of life. The question remains what the effects of common environment have influenced early age head circumference in the current results. Although pregnancy duration is significantly shorter in twin births (Buckler & Green, 1994; Green & Buckler, 2008), adding it as a covariate did not change the results. Other prenatal factors the may have influenced both twins' head size may lie in the mother's behavior during pregnancy. These may include benign effects, such as good nutrition and malign effects such as smoking during pregnancy. These factors are long known to influence birth weight or causing intra-uterine growth retardation (e.g., Kramer, 1987; Philipps & Johnson, 1977; Sexton & Hebel, 1984). These factors are prime candidates for future investigations into the early common environmental effects on head circumference.

A number of studies have identified large families with autosomal dominant inheritance of small head size (microcephaly; < 3rd percentile), in combination with normal intelligence (e.g., Merlob et al. 1988; Hennekam et al. 1992). Similar pedigrees with autosomal dominant inheritance of large head size (macrocephaly; > 97th percentile) have been reported (Asch and Meyers, 1976). One study of children with large heads showed that about half had a family history of large heads, and very few of these were retarded (Lorber & Priestly 1981). Although families with autosomal dominant inheritance are likely to exist, systematic analysis of parents of children with macrocephaly indicates that in the majority of cases macrocephaly is inherited as a multifactorial trait (Arbour et al. 1996).

A number of genetic syndromes are associated with macrocephaly in the presence of normal or near normal cognitive development. These include von Recklinghausen neurofibromatosis, Sotos syndrome, Gorlin basal cell nevus syndrome, and Cowden disease. The genes that underlie these syndromes encode basic signaling molecules that often directly impact on neuronal proliferation or differentiation. For instance, the gene that causes Cowden disease is *PTEN*. *PTEN*'s growth regulatory functions are primarily mediated via its lipid phosphatase activity, which antagonizes the effects of activated PI3-kinase in the nutritionally controlled insulin receptor pathway, thereby reducing protein synthesis and restraining cell and organismal growth (Goberdhan & Wilson, 2003). Analysis of a mouse model and of cellular systems indicated that *PTEN* regulates neuronal size in vivo in a cell-autonomous manner (Lachyankar et al. 2000). Another study using neuron-specific knockout in mice suggests that *PTEN* regulates the transition of differentiating neuroblasts to postmitotic neurons (Kwon et al., 2001).

About 40% of otherwise neurologically asymptomatic von Recklinghausen neurofibromatosis patients have macrocephaly, which may be mostly due to an increase in white matter volume (Steen et al. 2001. The *NF1* gene, which is mutated in von Recklinghausen neurofibromatosis, encodes a member of the ras/ERK/CREB pathway (Weeber & Sweatt, 2002).

Sotos syndrome is characterized by advanced skeletal maturation, which leads to increased linear growth in combination with macrocephaly. While adult height tends to be normal or only mildly increased, most patients still have large heads in adulthood. The *NSD1* gene encodes a nuclear receptor gene of largely unknown function. *NSD1* has a SET domain, which possesses intrinsic histone methyltransferase activity with specificity for Lys36 of histone H3 (H3-K36) and Lys20 of histone H4 (H4-K20) (Rayasam et al. 2003).

Nevoid basal cell carcinoma syndrome (NBCC; Gorlin syndrome), an autosomal dominant disorder is linked to 9q22.3-q31, and caused by mutations in PTC, the human homologue of the Drosophila patched gene. About half of Gorlin syndrome patients have macrocephaly, usually with normal intelligence (Kimonis et al. 1997). PTC functions as a receptor for sonic hedgehog in the cell, and therefore is involved in many cell-regulatory processes (Chen and Struhl, 1996).

A number of genes have been shown to cause inherited microcephaly in humans. Feingold syndrome is characterized by autosomal dominant inheritance of microcephaly with normal or near-normal intelligence, and limb malformations such as syndactyly. Approximately one in three Feingold syndrome patients have esophageal or duodenal atresia or both (Celli et al. 2003). Feingold syndrome is caused by haploinsufficiency of the *MYCN* gene (van Bokhoven et al. 2005). This suggests that multiple aspects of early embryogenesis and postnatal brain growth in humans are tightly regulated by *MYCN* dosage. In mice, *MYCN* was shown to be essential for normal neurogenesis, regulating neural progenitor cell proliferation, differentiation, and nuclear size (Knoepfler et al. 2002). It has been proposed that *MYCN* plays essential roles as a downstream effector of Sonic hedgehog proliferative effects in neural precursors of the cerebellum (Knoepfler & Kenney, 2006).

Several genes are now known to cause severe recessive microcephaly (MCPH) with moderate mental retardation when inactivated (Woods et al., 2005). There is evidence that at least some of these microcephaly genes are under continuing adaptive evolution in humans (Evans et al. 2005). The function of MCPH genes during neurogenic mitosis is unknown but is likely to be either (1) controlling the expansion of the neural progenitor pool or (2) involvement in the decision to switch from symmetric to asymmetric cell division. The cellular localization of three of the MCPH proteins CDK5RAP2, ASPM, and CENPJ is known to be centrosomal during mitosis. This suggests that the centrosome is an organelle of great importance during neurogenic mitosis (Woods et al., 2005).

Any of the processes involved in syndromic microcephaly or macrocephaly may play a role in regulating brain size and consequently head circumference in the normal population. Recent studies show that a significant proportion of all human genes show inherited cis-effects on expression levels (Cheung et al. 2005). Therefore, those genes that are known to have dosage sensitive effects on brain size, like *NSD1* and *MYCN* are prime candidates for the identification of genetic variation that regulates brain size in the normal population. However, in view of the limited success of candidate gene approaches in the area of complex traits related to brain and behavior (Sullivan) other approaches need to be considered also. The high heritability of indices of brain size suggests that genome-wide association studies might be successful in localizing and/or identifying genes that underlie the genetic variance. Due to the relative simplicity of its measurement, head circumference might be a valuable strategy to acquire an index of brain size in epidemiology-scaled samples.

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